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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/615,809	07/08/2003	Qi Huang	A-817	1461
30174	7590	11/14/2006	EXAMINER	
AMGEN INC. 1120 VETERANS BOULEVARD SOUTH SAN FRANCISCO, CA 94080			KOSACK, JOSEPH R	
			ART UNIT	PAPER NUMBER
			1626	

DATE MAILED: 11/14/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 10/615,809	<b>Applicant(s)</b> HUANG ET AL.	
	<b>Examiner</b> Joseph Kosack	<b>Art Unit</b> 1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 22 August 2006.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 1-3, 5-7, 9-11, 17, 19-24, 28-32 and 34-45 is/are pending in the application.
- 4a) Of the above claim(s) 21, 22, 28, 35 and 37-45 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 5-7, 9-11, 17, 19, 20, 23, 24, 29-31, 34 and 36 is/are rejected.
- 7) ☒ Claim(s) 32 is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |                                                                                                            |                                                                                         |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)                                | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                       | 5) <input type="checkbox"/> Notice of Informal Patent Application                       |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____                                                |

### **DETAILED ACTION**

Claims 1-3, 5-7, 9-11, 17, 19-24, 28-32, and 34-45 are pending in the instant application.

#### ***Amendments***

The amendment filed on August 22, 2006 has been acknowledged and has been entered into the application. The amendment filed August 11, 2006 was listed as non-compliant and has not been entered, however the arguments submitted then have been entered and have been considered for this office action.

#### ***Status of the Claims***

By virtue of the amendment filed on August 22, 2006, claims 20 and 31 are now within the scope of elected subject matter and is examined in this office action.

#### ***Previous Claim Objections***

Claims 1-12, 16-19, 23-27, 29-30, 32, 34, and 36 were objected to in the previous action for containing elected and non-elected subject matter. The objections have been withdrawn for claims 4, 8, 12, 16, 18, and 25-27 by virtue of the cancellation of those claims. The objection stands for claims 1-3, 5-7, 9-11, 17, 19, 23, 24, 29, 30, 32, 34, and 36 as non-elected subject matter remains for R<sup>2</sup>. The elected subject matter has not been expanded from the previous action since there are new art rejections based on the amendments to the claims.

#### ***Previous Claim Rejections - 35 USC § 102***

Claim 1 was rejected in the previous action under 35 U.S.C. 102(b) as being anticipated by Lockemann et al. (*Chemische Berichte* 1947, 485-493). The

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amendment to the claim has rendered the rejection moot, therefore the rejection is withdrawn.

Claims 1-2, 8, 10-12, 16-17, 19, 23-25, 29, and 36 were rejected in the previous action under 35 U.S.C. 102(b) as being anticipated by Huth et al. (WO 00/27819). The amendment to the claim has rendered the rejection moot, therefore the rejection is withdrawn.

Claims 1-4, 10-12, 16-17, 19, 23-25, 29, and 36 were rejected in the previous action under 35 U.S.C. 102(b) as being anticipated by Huth et al. (WO 00/27819). The amendment has not excluded 1,2,3,4-tetrahydroquinolyl, therefore the rejection stands. The rejection is withdrawn on claims 4, 12, 16, and 25 as those claims have been cancelled.

***Previous Claim Rejections - 35 USC § 103***

Claims 1-12, 16-17, 19, 23-25, 29-30, 32, 34, and 36 were rejected in the previous action under 35 U.S.C. 103(a) as being unpatentable over Altmann et al. (USPN 6,448,277). The amendment to the claim has rendered the rejection moot, therefore the rejection is withdrawn.

***Previous Double Patenting Rejections***

Claims 1-12, 16-17, 19, 23-25, 29-30, 32, 34, and 36 were rejected in the previous action under the doctrine of obviousness double patenting as being unpatentable over claims 1 and 7 of USPN 6,448,277. The amendment to the claim has rendered the rejection moot, therefore the rejection is withdrawn.

***Claim Objections***

Claims 1-3, 5-7, 9-11, 17, 19-20, 23, 24, 29, 30-32, 34, and 36 are objected to for containing elected and non-elected subject matter. The elected subject matter have been identified supra.

Claims 3 and 9 objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 3 and 9 have an expanded definition of  $R^1$  than base claim 2.

### ***Claim Rejections - 35 USC § 102***

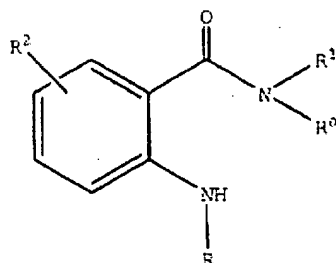
The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-3, 10-11, 17, 19-20, 23-24, 29, and 36 rejected under 35 U.S.C. 102(b) as being anticipated by Huth et al. (WO 00/27819).

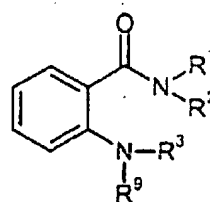
The instant application cites compounds of Formula I,



where:  $R$  is  $-(CH_2)_1-R^3$ ;  $R^3$  is a 6 membered ring with ring

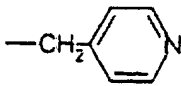
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members consisting of only carbon and nitrogen, optionally substituted as defined, optionally unsaturated as defined; and all other substituents are as defined.



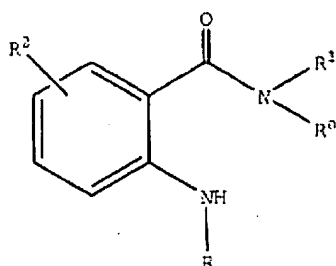
Huth et al. teach a compound with the formula:

where  $R^2$  and

$R^9$  are H,  $R^3$  is , and  $R^1$  is 7-1,2,3,4-tetrahydroquinolyl, which reads on the instant claims when R is  $-(CH_2)_1-R^3$ ,  $R^3$  is pyridyl,  $R^1$  is a 1,2,3,4-tetrahydroquinolyl and  $R^2$  and  $R^9$  are hydrogen. See Example 2.49 on page 45.

Claims 5-7 and 9 rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Huth et al. (WO 00/27819), Patani et al. (*Chem. Rev.* 1996, 3147-3176), Fotouhi et al. (US PG PUB 2002/0052512 A1), and of In re Wood (199 USPQ 137).

The instant application cites compounds of Formula I,



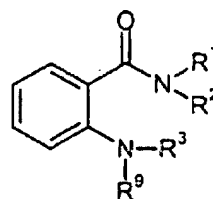
where: R is  $-(CH_2)_1-R^3$ ;  $R^3$  is a 6 membered ring with ring

members consisting of only carbon and nitrogen, optionally substituted as defined, optionally unsaturated as defined; and all other substituents are as defined. The claims

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are also drawn to pharmaceutically acceptable derivatives thereof, which are defined in the specification:

A "pharmaceutically-acceptable derivative" denotes any salt, ester of a compound of this invention, or any other compound which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to inhibit angiogenesis.



Huth et al. teach a compound with the formula:

where  $R^2$  and

$R^9$  are H,  $R^3$  is Cc1ccncc1, and  $R^1$  is indol-5-yl, or 4-chloropyridyl. See Examples 2.39 and 2.56 on pages 44-45.

Patani et al. teach ring replacements of NH for CH<sub>2</sub> in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles, as well as quinoline/isoquinoline, equivalent structures.

Fotouhi et al. teach that substituting and 2,3-dihydro-1H-indole for indole give molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2.

Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137.

If the term "indirectly" within the definition of "pharmaceutically-acceptable derivative" is construed to mean a compound that is an art-recognized equivalent that need not be the exact structure of the claimed compounds, then the claims would be

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rejected under 35 U.S.C. 102(b) as being anticipated and the additional citations would be merely to demonstrate that the cited compounds of Huth et al. are "pharmaceutically-acceptable derivative"

If the term "indirectly" within the definition of "pharmaceutically-acceptable derivative" is construed to mean a compound that when metabolized results in the exact structure of the claimed compounds, then the claims would be rejected under 35 U.S.C. 103(a) as being unpatentable and the additional citations would demonstrate bioisosteric replacements for the compounds of Huth et al. that are of knowledge to the person of ordinary skill in the art that would result in the claimed compounds with a reasonable expectation of success. The motivation provided by Patani et al. Patani et al. teach the ability of a group of bioisosteres to elicit similar biological activity has been attributed to common physicochemical properties. See page 3148.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.



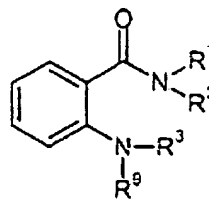
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 30 and 34 rejected under 35 U.S.C. 103(a) as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (*Chem. Rev.* 1996, 3147-3176) and of In re Wood (199 USPQ 137).

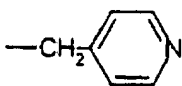
The instant invention is drawn to specific species of Formula 1'. Specifically, this rejection deals with N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[1-(2-[(2-methylamino-pyrimidin-4-ylmethyl)-amino]benzamide.

Determination of the scope and content of the prior art (MPEP §2141.01)



Huth et al. teach a compound with the formula:

where R<sup>2</sup> and

R<sup>9</sup> are H, R<sup>3</sup> is , and R<sup>1</sup> is 7-1,2,3,4-tetrahydroquinolyl. See example 2.49 on page 45.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Huth et al. do not teach pyrimidine for pyridine, tetrahydroisoquinolyl for tetrahydroquinolyl, or the methyl groups on the tetrahydroquinolyl.

Finding of prima facie obviousness--rational and motivation (MPEP §2142-2413)

Patani et al. teach ring replacements of NH for CH<sub>2</sub> in aromatic and aliphatic rings. See pages 3158-3159. This would make the pyridine/pyrimidine, as well as quinoline/isoquinoline, equivalent structures.

Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137.

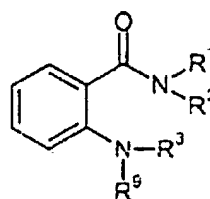
Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to follow the synthetic scheme of Huth et al. , make the bioisosteric replacements of Patani et al., and substitute methyl for hydrogen where needed in the tetrahydroisoquinolyl group to make the claimed invention with a reasonable expectation of success. The motivation to do so is provided by Patani et al. Patani et al. teach the ability of a group of bioisosteres to elicit similar biological activity has been attributed to common physicochemical properties. See page 3148.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

Claim 31 rejected under 35 U.S.C. 103(a) as being unpatentable over Huth et al. (WO 00/27819) in view of Patani et al. (*Chem. Rev.* 1996, 3147-3176), Fotouhi et al. (US PG PUB 2002/0052512 A1), and of In re Wood (199 USPQ 137).

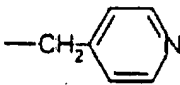
The instant invention is drawn to specific species of Formula 1'. Specifically, this rejection deals with N-(4,4-dimethyl-1,2,3,4-tetrahydro-isoquinolin-7-yl)-2-[1-(2-[(2-methylamino-pyrimidin-4-yl)methyl]-amino]benzamide.

Determination of the scope and content of the prior art (MPEP §2141.01)



Huth et al. teach a compound with the formula:

where R<sup>2</sup> and

R<sup>9</sup> are H, R<sup>3</sup> is , and R<sup>1</sup> is indol-5-yl. See example 2.56 on page 45.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Huth et al. do not teach pyrimidine for pyridine, tetrahydroisoquinolyl for tetrahydroquinolyl, or the methyl groups on the tetrahydroquinolyl.

Finding of *prima facie* obviousness--rational and motivation (MPEP §2142-2413)

Patani et al. teach ring replacements of NH for CH<sub>2</sub> in aromatic and aliphatic rings. See pages 3158-3159. This would make the 5-yl and 6-yl indoles equivalent structures.

Fotouhi et al. teach that substituting and 2,3-dihydro-1H-indole for indole give molecules with the same utility and comparable activities. See Example 315 on page 109, Example 38 on page 110, and the activities on page 136, column 2.

Hydrogen and methyl are deemed obvious variants. In re Wood, 199 USPQ 137.

Therefore, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to follow the synthetic scheme of Huth et al. , make the bioisosteric replacements of Patani et al., replace 2,3-dihydro-1H-indolyl for indole according to Fotouhi et al., and substitute methyl for hydrogen where needed in the tetrahydroisoquinolyl group to make the claimed invention with a reasonable expectation of success. The motivation to do so is provided by Patani et al. Patani et al. teach the ability of a group of bioisosteres to elicit similar biological activity has been attributed to common physicochemical properties. See page 3148.

Thus, the claimed invention as a whole was *prima facie* obviousness over the combined teachings of the prior art.

### **Conclusion**

Claims 1-3, 5-7, 9-11, 17, 19-20, 23-24, 29-31, 34, and 36 are rejected. Claims 1-3, 5-7, 9-11, 17, 19-20, 23, 24, 29, 30-32, 34, and 36 are objected to. Claim 32 appears to be free of the prior art.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

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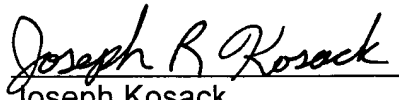
A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph Kosack whose telephone number is (571)-272-5575. The examiner can normally be reached on M-F 5:30 A.M. until 2:00 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on (571)-272-0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

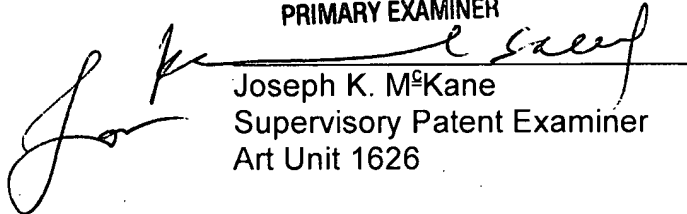
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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Joseph Kosack  
Patent Examiner  
Art Unit 1626

KAMAL A. SAEED, PH.D.  
PRIMARY EXAMINER



Joseph K. McKane  
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